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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/576,066	04/18/2006	Hirokazu Matsumoto	0233120123	2077

22428 7590 12/31/2007

FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
DUTT, ADITI	
ART UNIT	PAPER NUMBER
1649	

MAIL DATE	DELIVERY MODE
12/31/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	10/576,066	MATSUMOTO ET AL.
	Examiner	Art Unit
	Aditi Dutt	1649

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *3,10-16 and 23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-9 and 17-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 April 2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/18/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Appendix A, B*.

DETAILED ACTION

Status of Application, Amendments and/or Claims

1. The amendment of 12 October 2007 has been received and entered in full.

Election/Restrictions

2. Applicant's election **without traverse** of Group I, represented by claims 1-9 and 17-22, drawn to a monoclonal antibody reacting specifically with a polypeptide of SEQ ID NO: 1, a pharmaceutical composition and a diagnostic agent comprising the antibody, and a method of producing the antibody, in the reply filed on 12 October 2007 is acknowledged.

3. Applicant's election of SEQ ID NO: 1 under the secondary restriction requirement, will be considered for examination.

4. Claims 3, 10-16 and 23, are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 12 October 2007.

5. Claims 1-2, 4-9 and 17-22 are under consideration in the instant application.

Drawings

6. The drawings are objected to because:

"Y" axis should be appropriately labeled in Figure 8.

7. Figure 8 is also objected because legends are missing. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Objections

8. Claim 17 is objected to because of the following informalities:

Claim 17 depends from a non-elected claim 15.

Appropriate correction is required.

Claim Rejections

35 USC § 101 – Non-statutory subject matter

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

9. Claims 20-22 are rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter. The claims read on a product of nature in that the claimed antibody is not "isolated". In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. See Diamond v. Chakrabarty, 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "isolated", or "purified" or "monoclonal" or "polyclonal" or "labeled". See MPEP 2105.

Claim Rejections - 35 USC § 112-Second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 2, 17, and 20-22, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

11. Claim 2 is vague and unclear, because it is not ascertainable as to whether limitations corresponding to amino acid sequences of "8^{th} to 9^{th}, 11^{th}, 15^{th}..." recited in the claim, means "8^{th} to 9^{th}, 8^{th} to 11^{th}, 8^{th} to 15^{th}..", or "8^{th} to 9^{th}, 9^{th} to 11^{th}, 11^{th} to 15^{th}...". Clarification is requested.

12. Claim 17, is rejected because the claims recite the limitation "culturing the hybridoma ....in vivo .....and collecting the monoclonal antibody .....from the body fluid". It is not clear how the hybridoma can be **cultured in vivo** and **collected from the body fluid.**

13. Claims 20-22 are rejected for being vague and indefinite, as it is not clear whether "an antibody" is reacting with the binding site of the antibody OR it is reacting against a polypeptide.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 5 and 6 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

15. The invention appears to employ the human antibody, ZAL2-103 and ZAL2-106, obtained from hybridoma cell lines deposited under accession numbers of FERM BP-8431 and FERM-BP-8432 respectively (instant specification, page 2, lines 17-20; page 22, lines 31-35; page 23, lines 1-5). Since the antibodies are essential to the claimed invention, they must be obtainable by a repeatable method set forth in the specification or otherwise readily available to the public. The specification does not disclose a repeatable process to obtain the antibodies and it is not apparent if these are readily available to the public. It is noted that Applicant has deposited the hybridoma cell lines, as mentioned above, but there is no indication in the specification as to public availability. Hence, Applicants' referral to the two hybridoma deposits on

pages 22 and 23 of the specification is an insufficient assurance that all of the conditions of 37 CFR sections 1.801 through 1.809 have been met. If the deposits were made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by Applicants, assignees or a statement by an attorney of record over his or her signature and registration number stating that the deposits have been accepted by an International Depository Authority under the provisions of the Budapest Treaty, and that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves these specific matters to the discretion of each State.

16. Claims 8 and 18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

17. The specification does not reasonably provide enablement for a pharmaceutical composition comprising the monoclonal antibody to the amino acid sequence of SEQ ID NO: 1, to be used as an agent for the prevention and/or treatment of central nervous system (CNS), motor dysfunction or endocrine diseases.

18. The claims are directed to a pharmaceutical composition comprising the monoclonal antibody reacting with the amino acid sequence of SEQ ID NO: 1, and a pharmacologically acceptable carrier, that is used as an agent for the prevention and/or treatment of central nervous system (CNS), motor dysfunction or endocrine diseases.

19. The specification of the instant application teaches that human ZAQ ligand-2 or ZAQL-2 (also called Bv8 maturation peptide or prokinectin-2) having an amino acid sequence of SEQ ID NO: 1, are novel peptides localized in the rat suprachiasmatic nucleus, and inducing a circadian change when expressed (page 1, lines 14-27). The specification also teaches the making of monoclonal antibodies to SEQ ID NO: 1 or ZAQL-2, by culturing the hybridoma (page 23-27, Example 1). Furthermore, the instant specification speculates that the above antibody could be used for the prevention and/or treatment of a vast array of disorders (page 19, line 5-28). However, the specification does not provide enablement for a pharmaceutical composition comprising the antibody of the claimed invention. The specification does not teach how to use the antibody as a therapeutic for the prevention and/or treatment of any disease without undue experimentation. There are no methods or working examples directed to any particular disorder by administration of the antibody.

20. Furthermore, in making a determination of whether the application complies with the enablement requirement of 35 U.S.C. 112 first paragraph, each claimed invention must be evaluated to determine whether there is sufficient

guidance provided and supported by working examples to inform a skilled artisan how to use the claimed invention without undue experimentation. In the instant case, the specification provides no guidance on how to use the claimed method for the prevention and treatment of a variety of disorders, because there is no evidence or sound scientific reasoning presented in the case, that administration of the claimed antibody would be beneficial to prevent or treat symptoms of the diseases. Furthermore, even though ZAQL-2 peptide may be important for controlling apoptosis in vitro, there is no evidence that inhibition of peptide action using antibodies would successfully prevent or treat any disease, since the pathology of the diseases involves a cascade of steps and pathways.

21. Furthermore, the term 'preventing' (recited in the claims) corresponds to stopping of diseases. Relevant literature states that Bv8 addition to cerebellar granule cell culture reduces the apoptotic death of neurons by activating the mitogen-activated protein kinase (MAP kinase) and the phosphatidyl inositol-3-kinase pathways (Melchiorri et al. Eur J Neurosc 13: 1694-1702, 2001; Figure 4). The art also teaches that intracerebroventricular injection of recombinant prokinectin-2 in rats inhibits the nocturnal locomotor activity (Cheng et al. Nature 417: 405-410, 2002; Figure 6). However, the instant specification and the relevant art fail to provide specific guidance on the relationship of the antibody with any particular disease, target tissues and cells, mode of delivery, etc. to enable treatment and/or prevention of the disease/diseases. Since the pathophysiology of most of the CNS diseases are unknown, and the action of the

antibody associated with the disease is also unknown, prevention and treatment of the disease with success is highly unpredictable.

22. Due to the large quantity of experimentation necessary to prevent or treat any disease; the complex nature of the invention; the unpredictability of administering the antibody for therapeutic use in vivo and the state of the prior art which lacks information in this regard; undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

23. Claims 1-2, 4, 7-9, 17-20 are rejected under 35 U.S.C. 102(b) as clearly anticipated by Hinuma et al (International Patent Publication No. WO200262944-A2, published on 15 August 2002).

24. The claims recite a monoclonal antibody that specifically binds with a polypeptide of SEQ ID NO: 1, or specific sequences thereof (claims 1, 2, 20-22), wherein the antibody is labeled and has a neutralizing activity to the peptide of SEQ ID NO: 1 (claims 4, 7). The claims further recite a pharmacological composition and a diagnostic agent comprising the monoclonal antibody (claims 8, 9), which are agents for the prevention, treatment or diagnosis of various diseases, like CNS disorders, etc (claims 18, 19). Finally, the claims recite a method of producing the monoclonal antibody comprising culturing the hybridoma and collecting the antibody from the body fluid or culture (claim 17).

25. Hinuma et al. teach a peptide of SEQ ID NO: 39 that is 100% identical to the amino acid sequence of SEQ ID NO: 1 of the instant application (page 1, lines 6-10; see Appendix A for sequence alignment). Hinuma et al further teach specific monoclonal antibodies to the above peptide, partial peptides or salts thereof (page 41, lines 29-34), that can be prepared from monoclonal antibody producing hybridomas by cultivating the hybridoma and determining the antibody titer in the culture supernatant (page 43, lines 10-22). Furthermore, Hinuma et al teach screening of the monoclonal antibody producing hybridoma by adding an anti-mouse immunoglobulin antibody for the detection of the claimed monoclonal antibody bound to the solid phase (page 43, lines 2-5). The reference also teaches the use of labeled antibody for quantification of the peptide of the invention in immunoassays (page 79, lines 2-4, 12-14). The antibody can be used for detection of the peptide in the diagnosis of various diseases, such as

digestive diseases, central nervous diseases, etc. (page 82, lines 4-18). Finally, the reference teaches that the antibody can be used as a pharmaceutical and diagnostic agent, for digestive diseases, central nervous diseases etc. (page 84, lines 29-35; page 85, lines 1-17; page 132, lines 17-18, 24-25, 27-29). It is to be noted that since the antibody is anticipated to be used for treatment of several diseases, it inherently has the property of binding to the polypeptide, and inhibiting specific activities relevant to disease control or amelioration, thereby functioning as a neutralizing antibody. It is further noted that since the antibody of the reference is specifically binding to the peptide as stated above, it would inherently bind to the specific domains of the peptide (as recited in claim 2 of the instant application). That the reference is silent on the binding domains does not prove otherwise. Thus Hinuma et al anticipate the claimed invention.

26. Claims 1-2, 4, 7-9, 17-20 are rejected under 35 U.S.C. 102(e) as clearly anticipated by Sheppard et al (US Patent No. 6,828,425 B2, filed 2 August 2002).

27. Sheppard et al. teach a peptide Zven1 (SEQ ID NO: 2), wherein the peptide sequence comprising 28-108 amino acids is 100% homologous to SEQ ID NO: 1 of the instant invention (See Appendix B for sequence alignment), and monoclonal antibodies that specifically bind to the above Zven1 peptide (col 4 lines 50-55; also see claim 14). Sheppard et al. also teach that monoclonal antibodies can be obtained by culturing and isolating form the hybridoma culture

(col 46, lines 56-64). The reference further teaches labeled antibodies for immunochemical detection of the peptide, which can either be an antibody moiety that binds to the anti Zven antibody, or conjugated with a detectable molecule (col 53, lines 8-29). Finally the reference teaches diagnostic kits and pharmaceutical compositions comprising the antibody and a pharmaceutically acceptable carrier (col 54, lines 33-36; col 57, lines 16-20). As stated above the limitations of neutralizing antibody and specific domains for antibody binding are inherent for reasons explained above. Thus Sheppard et al anticipate the claimed invention.

Conclusion

28. No claims are allowed.

29. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aditi Dutt whose telephone number is (571) 272-9037. The examiner can normally be reached on Monday through Friday, 9:00 a.m. to 5:00 p.m.

30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

31. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov/. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AD
20 December 2007

GARY B. NICKOL, PH.D.
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

APPENDIX - A.

<!--StartFragment-->RESULT 3
ABG94398
ID ABG94398 standard; protein; 81 AA.
XX
AC ABG94398;
XX
DT 27-NOV-2002 (first entry)
XX
DE Human GPCR ligand Bv8 protein sequence #2.
XX
KW G-protein coupled receptor; GPCR; ZAQ; human; ZAQC; ZAQT; rat; ZAQ1;
KW rZAQ1; rZAQ2; mouse; I5E receptor; mI5E; GPR73; Bv8 protein; MIT1;
KW digestive disorder; central nervous system disorder; CNS; diarrhoea;
KW bowel inflammation; constipation; food absorption disorder; nootropic;
KW Alzheimer's disease; Parkinson's disease; schizophrenia; laxative;
KW antiinflammatory; antidiarrhoeic; neuroleptic; neuroprotective; receptor.
XX
OS Homo sapiens.
XX
PN WO200262944-A2.
XX
PD 15-AUG-2002.
XX
PF 01-FEB-2002; 2002WO-JP000852.
XX
PR 02-FEB-2001; 2001JP-00026820.
XX
PA (TAKE) TAKEDA CHEM IND LTD.
XX
PI Ohtaki T, Masuda Y, Takatsu Y, Watanabe T, Terao Y, Shintani Y;
PI Hinuma S;
XX
DR WPI; 2002-627537/67.
DR N-PSDB; ABS71104.
XX
PT Screening of compounds modifying the binding of G-protein coupled
PT receptor protein ZAQ and related proteins to their ligands for use in
PT treatment and diagnosis of digestive disorders.
XX
PS Claim 1; Page 165; 197pp; Japanese.
XX
CC The present invention relates to a screening method for compounds for
CC their ability to modify the binding of G-protein coupled receptor (GPCR)
CC protein ZAQ and related proteins (human ZAQC, human ZAQT, rat ZAQ1
CC (rZAQ1), rZAQ2, human and mouse I5E (mI5E) receptor, and mouse GPR73) to
CC their ligands (the mature form of human, mouse or rat Bv8 protein). The
CC receptor protein and ligand are contacted in the presence or absence of
CC the test compound. The compounds are useful in a drug composition for the
CC treatment, and prevention of digestive and central nervous system (CNS)
CC disorders, including bowel inflammation, diarrhoea, constipation, food
CC absorption disorders, Alzheimer's disease, Parkinson's disease and
CC schizophrenia. The present sequence represents a GPCR or related protein
XX
SQ Sequence 81 AA;

Query Match 100.0%; Score 461; DB 5; Length 81;
Best Local Similarity 100.0%; Pred. No. 6e-41;
Matches 81; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

```
Qy          1 AVITGACDKDSQCGGGMCCAVSIWVKSIRICTPMGKLGDSCHPLTRKVPFFGRRMHHTCP 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 AVITGACDKDSQCGGGMCCAVSIWVKSIRICTPMGKLGDSCHPLTRKVPFFGRRMHHTCP 60

Qy         61 CLPGLACLRTSFNRFICLAQK 81
              |||||||||||||||||||||
Db         61 CLPGLACLRTSFNRFICLAQK 81
```

<!--EndFragment-->

APPENDIX-B

```
<!--StartFragment-->RESULT 5
US-10-212-355-2
; Sequence 2, Application US/10212355
; Patent No. 6828425
; GENERAL INFORMATION:
;  APPLICANT: Sheppard, Paul O.
;  APPLICANT:  Bishop, Paul D.
;  APPLICANT:  Whitmore, Theodore E.
;  APPLICANT:  Thompson, Penny P.
;  TITLE OF INVENTION: Human Zven Proteins
;  FILE REFERENCE: 99-81
;  CURRENT APPLICATION NUMBER: US/10/212,355
;  CURRENT FILING DATE:  2002-08-02
;  NUMBER OF SEQ ID NOS: 7
;  SOFTWARE: FastSEQ for Windows Version 3.0
; SEQ ID NO 2
;   LENGTH: 108
;   TYPE: PRT
;   ORGANISM: Homo sapiens
US-10-212-355-2

  Query Match             100.0%;  Score 461;  DB 2;  Length 108;
  Best Local Similarity   100.0%;  Pred. No. 1.4e-43;
  Matches   81;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 AVITGACDKDSQCGGGMCCAVSIWVKSIRICTPMGKLGDSCHPLTRKVPFFGRRMHHTCP 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         28 AVITGACDKDSQCGGGMCCAVSIWVKSIRICTPMGKLGDSCHPLTRKVPFFGRRMHHTCP 87

Qy         61 CLPGLACLRTSFNRFICLAQK 81
              |||||||||||||||||||||
Db         88 CLPGLACLRTSFNRFICLAQK 108
<!--EndFragment-->
```